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Unexplained reciprocal regulation of diabetes and lipoproteins

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Abstract

Purpose of review—Type 2 diabetes is associated with a characteristic dyslipidemia that may exacerbate cardiovascular risk. The causes of, and the effects of new antihyperglycemia medications on, this dyslipidemia, are under investigation. In an unexpected reciprocal manner, lowering LDL-cholesterol with statins slightly increases the risk of diabetes. Here we review the latest findings.

Recent findings—The inverse relationship between LDL-cholesterol and diabetes has now been confirmed by multiple lines of evidence. This includes clinical trials, genetic instruments using aggregate single nucleotide polymorphisms, as well as at least eight individual genes – *HMGCR, NPC1L1, HNF4A, GCKR, APOE, PCKS9, TM6SF2,* and *PNPLA3* – support this inverse association. Genetic and pharmacologic evidence suggest that HDLcholesterol may also be inversely associated with diabetes risk. Regarding the effects of diabetes on lipoproteins, new evidence suggests that insulin resistance but not diabetes per se may explain impaired secretion and clearance of VLDL-triglycerides. Weight loss, bariatric surgery, and incretin-based therapies all lower triglycerides, whereas SGLT2 inhibitors may slightly increase HDL-cholesterol and LDL-cholesterol.

Summary—Diabetes and lipoproteins are highly interregulated. Further research is expected to uncover new mechanisms governing the metabolism of glucose, fat, and cholesterol. This topic has important implications for treating type 2 diabetes and cardiovascular disease.

Keywords

diabetes; HDL; LDL; statins; triglycerides

INTRODUCTION

Type 2 diabetes has long been known to be associated with a characteristic dyslipidemia, including high triglycerides, small/dense LDL particles, and low levels of HDL-cholesterol

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Conflicts of interest

There are no conflicts of interest.

[1]. However, the mechanisms underlying the effects of diabetes on dyslipidemia are incompletely understood. Moreover, recent data have revealed a surprising converse association, whereby some lipoproteins appear to impact diabetes diagnosis or severity (Fig. 1). The goals of this article are to review the data surrounding the effects of lipoproteins on diabetes risk, and to summarize new updates within the last 2 years on the effects of diabetes on lipoproteins.

LOW LDL-CHOLESTEROL IS LINKED TO INCREASED DIABETES RISK

Several years ago, it was revealed that statins, widely used for LDL lowering, are associated with a slightly higher risk of diabetes [2,3,4■]. This risk is statin dose-dependent [5]. In patients with established diabetes, statin usage is associated with increased hemoglobin A1c (HbA1c), though the effect is small [6,7]. These findings provoked the question of whether inhibition of HMGCR – the statin mechanism of action – was to blame for impaired glycemia. Indeed, genetic variants in the *HMGCR* gene that lower LDL-cholesterol tend to be associated with slightly increased diabetes risk [8,9,10■■]. However, it remained unclear whether this was specific to HMGCR, or was triggered by other methods of LDL-cholesterol modulation. Support for the latter came from Fall *et al.* [11], who used a genetic instrument containing 140 single nucleotide polymorphisms (SNPs) – in genes other than *HMGCR* – to show that higher LDL-cholesterol is associated with a lower diabetes risk, although an earlier study using 31 SNPs found no effect on diabetes risk [12]. A summary of the effects of lipoproteins on diabetes is shown in Table 1.

Recent evidence confirming the link between LDL-cholesterol and diabetes—

Over the last 2 years, significant progress has been made, particularly through the use of genetics. Mendelian randomization (based on 130 SNPs) demonstrated that genetic risk for increased LDL-cholesterol increases coronary artery disease risk and lowers type 2 diabetes risk [13]. Likewise, there is an inverse correlation between the effects of 113 coding variants on LDL-cholesterol and type 2 diabetes [14]. However, the substantial heterogeneity in this effect highlights that associations between LDL-cholesterol and diabetes may be mechanism-specific.

Individual genes associated with LDL-cholesterol have been queried (Table 1). In addition to *HMGCR*, at least seven other loci are associated with both lower LDL-cholesterol and higher diabetes risk. This includes *NPC1L1, HNF4A,* and *GCKR* [10■■,14], and multiple variants in or near *APOE* [14–16]. The same holds for variants at *PCSK9* [9,10■■,14,17]. It is worth noting that individual studies of PCSK9 inhibitors have not shown an effect of these drugs on glycemia or diabetes diagnosis [18–24]. However, the follow-up periods in these studies were all 2.2 years or less, and a meta-analysis across 20 PCSK9 inhibitor trials did identify increases in plasma glucose and HbA1c, in proportion to LDL-cholesterol-lowering [25■■]. Two additional gene variants, in *TM6SF2* and *PNPLA3*, were recently found to be associated with low LDL-cholesterol and increased type 2 diabetes in a study of more than 300 000 individuals [14]. The small effect size may explain why multiple smaller prior studies did not find any effect of these variants on insulin sensitivity [26]. Supporting the idea of mechanism-specific effects is the finding that an LDL-cholesterol-modulating allele in *APOB* showed no relationship with diabetes risk [27].

Importantly, in addition to LDL-cholesterol, some of these variants are associated – sometimes more strongly – with other metabolic traits. For example, *GCKR, TM6SF2,* and *PNPLA3* are all associated with high liver fat [14]. Given the well established correlation between liver fat and insulin resistance, it would be reasonable to predict that for these variants, high liver fat – rather than LDL-cholesterol – is the driver of increased diabetes risk. However, for statins in particular, at least one analysis implicates LDL-cholesterol-lowering as the key mediator [28]. Ultimately, mechanistic investigations are required to establish the causal links.

Do other lipoproteins contribute to diabetes risk?—Several studies have used multivariate regression analyses using simple clinical measurements to identify that low HDL-cholesterol and high triglycerides can significantly predict diabetes [29–34]. New publications move beyond these biomarker analyses to ask whether HDL-cholesterol and triglycerides could be causative factors in diabetes development.

The enzyme cholesteryl ester transfer protein (CETP) transfers cholesterol from HDL particles onto triglyceride-rich lipoproteins. Therefore, inhibitors of CETP raise HDL-cholesterol and lower LDL-cholesterol. Based on the effects of low LDL-cholesterol described above, one might predict CETP inhibitors would worsen glycemia. On the contrary, two different inhibitors of CETP, as well as genetic *CETP* deficiency, are associated with improved glycemia [35]. Moreover, recent data from the REVEAL trial – which had 4.1 years of follow-up – showed that Anacetrapib raised HDL-cholesterol and lowered LDL-cholesterol while reducing new-onset diabetes and HbA1c [36■■]. These findings suggest the possibility that CETP inhibition, or raising HDL-cholesterol more generally, has a beneficial effect on glycemia that is independent of, or counteracts against, the effects of LDL-cholesterol-lowering.

In support of this, three independent studies used genetic instruments of SNPs associated with high HDL-cholesterol and found them to be associated with lower diabetes risk [11–13]. Furthermore, genetically determined increases in cholesterol specifically on large and extra-large HDL particles is associated with lower fasting glucose [37]. In contrast, an independent study showed no effect of HDL-cholesterol on diabetes risk [38].

Data on the effects of plasma triglycerides on glycemia are more varied. One study of more than 300 000 people found that variants in *LPL* and *ANGPTL4* that lower triglycerides also lower diabetes [14]. Two others also found that genetically high triglycerides associate with increased diabetes risk [12,37]. However, three studies did not find conclusive effects [11,13,39]. Experiments in preclinical models suggest an important role for the metabolism of triglyceride-rich lipoproteins by lipoprotein lipase (LPL) in the regulation of body weight and glycemia. Several years ago it was shown that LPL promotes uptake of triglycerides from chylomicrons into the hypothalamus, and that deficiency of neuronal LPL causes obesity [40]. Recent studies have extended this finding, showing that LPL deficiency specifically in the mediobasal hypothalamus [41], or in astrocytes [42], or in microglia [43], all cause increased obesity and worse glycemia.

Causative mechanisms—Plausible mechanisms linking low lipoprotein-cholesterol to worsening glycemia are limited. A few potential cellular mechanisms have been proposed [44]. One invokes cell membrane fluidity: perhaps low circulating cholesterol would impact plasma membrane composition or microdomains and impair the localization or function of glucose transporters or signaling receptors. A second possibility indicts intracellular cholesterol metabolism. Inhibition of HMGCR decreases production of not only cholesterol, but also other products of the mevalonate pathway such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These two lipids help form membrane anchors, and dampening their production may impair plasma membrane protein localization. However, the cell-types and the plasma membrane proteins that would potentially be involved have not yet been defined.

Recent publications report new roles for hepatocellular cholesterol homeostasis on insulin-regulated pathways, although none implicate lipoprotein-cholesterol per se. One suggests – in conceptual contrast to the prediction cited above – that hepatocyte accumulation of mevalonate pathway intermediates, caused by impaired cholesterol catabolism, is linked to increased glucose production [45]. However, the direct molecular mediators of this link are not yet defined. Moreover, one of the proposed players – the cholesterol-catabolizing enzyme CYP7A1 – was shown to have the opposite effect on glucose metabolism *in vivo* [46]. Thus, the role of this pathway in linking cholesterol with glycemia remains uncertain. Ablating the sinusoidal hepatocyte cholesterol efflux transporter *Abca1* impairs insulin signaling [47]. However, this impairment was specific for insulin-regulated lipogenesis, without affecting gluconeogenesis. Thus, these studies of hepatocellular cholesterol catabolism and efflux have not yet yielded clear hypotheses linking low lipoprotein-cholesterol and glucose homeostasis.

Perhaps other, nonhepatocyte cell types are involved. One candidate would be macrophages, as they take up LDL particles. However, data do not yet support this prediction. Reducing cholesterol content in myeloid cells, by ablating the enzyme fatty acid synthase, reduces inflammatory signaling and actually *improves* insulin sensitivity during high fat feeding [48]. Macrophages also efflux cholesterol onto HDL; could this reveal a link? Transplanting wild-type mice with bone marrow from mice lacking the cholesterol efflux transporter *Abca1* worsens high fat diet-induced insulin resistance [49]. However, the opposite conclusion was reached after transplanting bone marrow transplant from mice lacking both efflux transporters *Abca1* and *Abcg1*; these mice showed improved glucose parameters [50]. Thus, macrophage cholesterol handling is not a clear link between lipoproteins and glycemia.

Another candidate cell-type would be pancreatic β-cells, as a substantial portion of diabetes risk is attributed to β-cell function or survival. Multiple lines of evidence suggest that increased β-cell cholesterol accumulation impairs insulin secretion [51,52,53]. Notably, humans with mutations in *ABCA1* also have impaired insulin secretion [54]. This might suggest a mechanism whereby low HDL-cholesterol is a marker for impaired cholesterol efflux causing β-cell cholesterol accumulation and defective insulin secretion. However, this would not explain the benefit of CETP inhibitors or *CETP* deficiency, as these affect circulating lipoprotein particles, nor would it explain effects of LDL-cholesterol.

Overall, studies over the last few years have solidly demonstrated that LDL-cholesterol lowering by pharmacotherapy or genetic variation causes increased risk of type 2 diabetes, whereas HDL-cholesterol raising may be protective. It is important to note the much greater benefit of lowering LDL-cholesterol for reducing cardiovascular events is considered to outweigh the small risk of diabetes [55]. However, the molecular mechanisms of this effect are almost completely obscure, and understanding these biological underpinnings may aid in the design of future drugs or in the identification of the minority of patients who are at risk and should be given alternative cardioprotective therapies.

IMPACT OF DIABETES ON LIPOPROTEIN METABOLISM

The pro-atherogenic lipid profile associated with diabetes is evident even before the diagnosis of diabetes, in the states of insulin resistance or impaired fasting glucose [56,57]. However, the metabolic and molecular mechanisms responsible for these phenotypes remain under debate. New studies shed light on the effects of diabetes and diabetes therapies on lipoproteins, and these are summarized here (Table 2).

Effects on lipoproteins in the natural history of diabetes

New kinetic studies have added to our understanding of VLDL-triglycerides, which are influenced by both secretion and clearance [58]. Nielsen *et al.* assessed VLDL kinetics in male type 2 diabetes patients and healthy controls [59▪,60,61]. In contrast to prior studies, the two groups were matched for body mass index. Surprisingly, VLDL-triglyceride secretion, clearance, and oxidation were the same between the two groups [59▪,60]. The effects of insulin or a mixed meal to suppress VLDL-triglyceride secretion were also comparable. Moreover, there were no differences in the ability of VLDL-triglyceride to be stored in adipose tissue [60]. These findings suggest that VLDL-triglyceride kinetics may be affected more strongly by obesity or insulin resistance than by diabetes per se. One of the only differences observed in diabetes patients was impaired suppression of apoB-100 secretion by insulin [59▪]. Perhaps this suggests a contributor to the accumulation of small, dense LDL particles.

Hypotheses to explain the overproduction and impaired clearance of VLDL-triglycerides during insulin resistance are summarized in references [57,62,63]. These include increased flux of free fatty acids from adipose to liver, as a consequence of poor insulin suppression of lipolysis, or increased hepatic lipogenesis. A new suggested mechanism for impaired clearance of triglyceride-rich lipoproteins in diabetes implicates the membrane raft protein flotillin-1, which is required for syndecan-1-mediated lipoproitein endocytosis, and which is strongly reduced in a mouse model of type 2 diabetes [64▪▪].

Effects of diabetes therapies on lipoproteins

Weight loss is a known method for improving diabetes and dyslipidemia [65], and new publications support this. Body weight loss of even 5–7% is sufficient to lower triglycerides, and further weight loss causes greater improvements [66–68]. Bariatric surgeries also lower triglycerides [69], as highlighted by recent publications [70–73]. Most weight loss interventions are also associated with increased HDL-cholesterol [67,68,70–73], and in the

case of sleeve gastrectomy, this may be consequent to enhanced HDL cholesterol efflux capacity [74]. However, weight re-gain reverses the improvements in lipoproteins [67]. Changes in LDL-cholesterol in response to weight loss were minor or absent in these studies, except a study of gastric bypass patients, 12 years after surgery [71].

Incretin-based antidiabetes therapies – including agonists of the glucagon-like peptide-1 (GLP-1) receptor and inhibitors of DPP-4, the enzyme responsible for degradation of GLP-1 and other incretins – have been scrutinized for their effects on cardiovascular risk. These drugs have been found to modestly improve lipoprotein profiles, by reducing chylomicron production, without affecting lipoprotein clearance [75–77]. The molecular mechanisms are unclear, but may be pharmacologic, as endogenous GLP-1 and GLP-2 appear to be minor contributors to postprandial chylomicron production [78]. Moreover, the potential lipid-lowering benefits of these drugs do not necessarily correlate with improvements in cardiovascular outcomes: two have successfully lowered major adverse cardiovascular events [79,80], but five have not [81–85], though all are confirmed to be safe [86]. It is possible that future drugs targeting these pathways can be designed to have greater lipid-lowering effects. Indeed, a dual agonist for both GLP-1 receptor and the glucose-dependent insulinotropic peptide (GIP) receptor lowers total cholesterol, potentially through the GIP signaling pathway [87].

Inhibitors of sodium-glucose transporter 2 (SGLT2) have also been assessed in recent years, and two have shown cardioprotective effects [88,89]. Though the mechanisms of this protection are unlikely to involve lipoproteins [90,91], it is still interesting to inspect the impact of these drugs on lipoproteins. Triglycerides tend to be reduced with SGLT2 inhibition, although differences are not reported in all studies [92,93]. More consistently reported are increases in HDL-cholesterol and LDL-cholesterol [89,92,93]. What are the causes of these effects? Decreases in triglycerides and increases in HDL-cholesterol could be attributable to the weight loss observed after SGLT2 inhibition. However, the cause of increased LDL-cholesterol is unknown. It could involve the effect of SGLT2 inhibitors to switch hepatic fuel selection towards fatty acid oxidation and ketogenesis [94,95], as a recent study suggests that ketogenic flux secondarily increases hepatocyte cholesterol synthesis, thus lowering LDL receptor and impairing LDL particle clearance [96].

CONCLUSION

The interrelationships between diabetes and lipid metabolism are complex. Basic biomedical investigations into these pathways are essential to fully understand these links and their consequences on the substantial portion of adults that are at risk for metabolic diseases.

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KEY POINTS

- Low levels of LDL-cholesterol are associated with increased type 2 diabetes risk
- HDL-cholesterol may also be inversely associated with diabetes risk
- The biological underpinnings of these effects are unknown
- Lipoprotein metabolism is altered in the natural history of diabetes, and in response to diabetes therapies

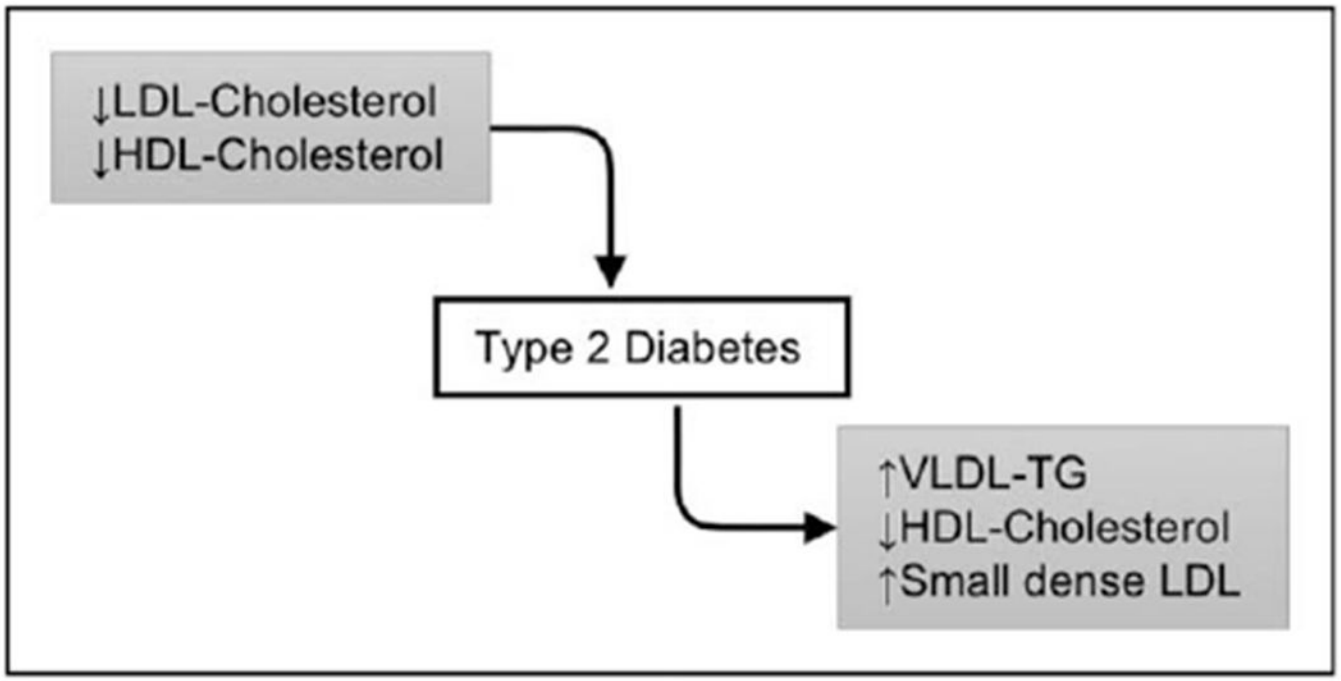

FIGURE 1.

Diabetes and lipoprotein metabolism are inter-regulated. Low levels of LDL-cholesterol and HDL-cholesterol increase type 2 diabetes risk and worsen glycemia. Type 2 diabetes is accompanied by abnormalities of lipoprotein metabolism.

Table 1.

Effects of lipoproteins on type 2 diabetes

References	Drug/genes	Effect on lipoprotein	Effect on T2D/glycemia
[2,3,4■,5–7]	Statins	LDL-C ↓	T2D ↑, HbA1c↑
[18–24,25■■]	PCSK9 inhibitors	LDL-C ↓	↔ or HbA1c↑
[11]	140 SNPs	LDL-C ↑	T2D ↓
[13]	130 SNPs	LDL-C ↑	T2D ↓
[12]	31 SNPs	LDL-C ↑	↔
[14]	113 SNPs	LDL-C ↓	T2D ↑
[8,9,10■■]	*HMGCR*	LDL-C ↓	T2D ↑
[10■■]	*NPC1L1*	LDL-C ↓	T2D ↑
[14]	*HNF4A*	LDL-C ↓	T2D ↑
[14]	*GCKR*	LDL-C ↓	T2D ↑
[14–16]	*APOE*	LDL-C ↓	T2D ↑
[9,10■■,14,17]	*PCSK9*	LDL-C ↓	T2D ↑
[14,26]	*TM6SF2*	LDL-C ↓	↔ or T2D ↑
[14,26]	*PNPLA3*	LDL-C ↓	↔ or T2D ↑
[27]	*APOB*	LDL-C ↓	↔
[35,36■■]	CETP inhibitors	HDL-C ↑, LDL-C ↓	T2D ↓, Glycemia ↓
[11]	140 SNPs	HDL-C ↑	T2D ↓
[13]	140 SNPs	HDL-C ↑	T2D ↓
[12]	41 SNPs	HDL-C ↑	T2D ↓
[38]	9 SNPs	HDL-C ↓	↔
[35]	*CETP*	HDL-C ↑	Glucose ↓
[13]	140 SNPs	TG ↑	↔ or T2D ↓
[11]	140 SNPs	TG ↑	↔ or T2D ↑
[12]	25 SNPs	TG ↑	T2D ↑
[39]	10 SNPs	TG ↑	↔
[14]	*LPL*	TG ↑	T2D ↑
[14]	*ANGPTL4*	TG ↑	T2D ↑

HbAlc, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SNPs, single nucleotide polymorphisms; T2D, type 2 diabetes; TG, triglycerides.

Table 2.

Recent data on the effects of diabetes or diabetes treatments on lipoproteins

References	Condition/treatment	TG	LDL	HDL
[57]	T2D, insulin resistance	VLDL-TG ↑	Small dense LDL↑	HDL-C ↓
[97]	T2D, obese vs. healthy, lean	VLDL-TG secretion ↑, LDL-TG clearance↓		
[59▪,60]	T2D, obese vs. bese, no diabetes	VLDL-TG secretion ↔, VLDL-TG clearance↔	Insulin suppression of apoB-100 secretion ↓	
[66–68]	Weight loss	TG↓		HDL-C↑
[70–73]	Bariatric surgeries	TG↓	LDL-C↔ or ↓	
[74]	Sleeve gastrectomy			HDL cholesterol efflux capacity↑
[67]	Weight regain after loss	TG↑		HDL-C↓
[77]	GLP-1 receptor agonist	TG↓	LDL-C↓	
[75,76]	DPP-4 inhibitor	TG↓	LDL particle size↑	
[89,92,93]	SGLT2 inhibitor	TG↔ or ↓	LDL-C↑	HDL-C↑

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes; TG, triglycerides; VLDL, very low-density lipoprotein.